CONSENSUS GUIDELINES FOR THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

Brazilian Study Group of Inflammatory Bowel Diseases*

ABSTRACT - This is the first Brazilian Consensus on inflammatory bowel disease, carried out by the Brazilian Study Group of Inflammatory Bowel Disease, and discusses the treatment of Crohn’s disease and ulcerative colitis in acute and remission phases. The first part of the text, brings out a review on the main drugs used in the treatment of inflammatory bowel disease, as well as their mechanisms of action and cautions during their use. In the second part, the committee’s opinions about the most recommended medical and surgical approaches for both diseases are presented on the basis of disease activity, location and behaviour status. The recommendations here presented were widely discussed in several scientific meetings with active participation of all members of the group and were highly based on scientific evidence covered by the literature.


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1. INTRODUCTION

Crohn’s disease (CD) and ulcerative colitis (UC) are the main inflammatory bowel diseases. They are caused by the interaction of genetic factors, intestinal microbiota and mucosal immunoregulation \[12, 24, 45, 81\].

UC compromises the rectum and colon, whereas CD may occur in any part of the digestive tract, from the mouth to the anus, but the ileal and ileocecal region are its main targets. CD involves the whole intestinal wall (transmural inflammation) and causes a non-caseating granulomatous reaction.

UC clinical picture depends on the extent and severity of the disease. UC is best evaluated using a colonoscopy (Figure 1), while its severity, by means of a clinical evaluation or using the Truelove and Witts index (Figure 2).

FIGURE 1. Ulcerative colitis (UC) classification according to the anatomic extension of the inflammation (colonicoscopic evaluation)

| Distal UC | Proctitis- inflammation of the rectal mucosa within 15 cm of the dentate line |
| Proctosigmoiditis – mucosal inflammation of the mucosa within 25–30 cm of the dentate line |
| Left-sided UC | Mucosal inflammation up to splenic flexure (sometimes up to distal transverse colon) |
| Pancolitis | Mucosal inflammation up to proximal transverse colon and beyond |

FIGURE 2. Classification of nonspecific ulcerative colitis (UC) according to severity of acute episode (Truelove & Witts\[95\])

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Number of evacuations/day</td>
<td>≤4</td>
<td>≥5 ≥26</td>
</tr>
<tr>
<td>2. Bright-red blood in stool</td>
<td>a</td>
<td>+</td>
</tr>
<tr>
<td>3. Temperature (°C)</td>
<td>Normal</td>
<td>Intermediate values</td>
</tr>
<tr>
<td>4. Pulse (bpms)</td>
<td>Normal</td>
<td>Intermediate</td>
</tr>
<tr>
<td>5. Hemoglobin(g/dL)</td>
<td>&gt; 10</td>
<td>Intermediate</td>
</tr>
<tr>
<td>6. *HSS (mm, 1st hour)</td>
<td>≤30</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>

\*HSS = Hemosedimentation speed

An easy way to classify UC as severe is to consider six or more bloody evacuations a day with at least one of the following alterations: a) fever (> 37.5°C); b) tachycardia (> 100 bpms); c) anemia (red blood cells < 10 g/dL); d) HSS > 30 mm, 1st hour; e) albumina < 3.5 g/dL. \[6\]

Fulminant UC is diagnosed when the patient has more than 10 bloody evacuations (enterorrhagia), fever, tachycardia, need for blood transfusion, marked alterations in inflammatory bowel disease (IBD) activity tests (e.g., HSS > 30 mm, 1st hour), with or without toxic megacolon, (dilated transverse colon > 6 cm) or intestinal perforation.

UC is evaluated according to the extension of the disease, as follows:

a) **Distal UC**: usually mild and moderate cases often with rectal bleeding and mucus and pus in stool and tenesmus. Diarrhea occurs in 80% of cases, however there may be constipation. Abdominal pain is usually cramp-like, preceding evacuations and is not fully relieved after colon rectal emptying. Patients may complain of urgency, incontinence and anorectal pains. Extraintestinal manifestations are less frequent (Figure 3).

b) **Left-sided hemicolon UC and pancolitis**: in such cases, patients usually suffer from moderate or severe forms of the disease. Fever, asthenia and weight loss with anorexia are common. Diarrhea with mucus, pus, blood and tenesmus may also be present. The fulminant form may occur. Extraintestinal manifestations happen in 20% to 30% of cases (for example: arthralgia, arthritis, sacroilitis, oral aphtae, nodous erythema, episcleritis and gangrenous pyoderma).

CD can also be classified according to severity, extension and disease behavior \[82\]. There are several activity indexes for CD and CDAI (Crohn’s Disease Activity Index) \[99\] (Figure 4) is the most used in clinical studies. However, in clinical practice the doctor’s impression is enough to evaluate the severity of the disease. Such impression must consider location, extension, behavior, age, extraintestinal manifestations and the patient’s life history.

More recently the Montreal classification (modified from the Vienna classification) was described so as to homogenize case description mainly in clinical studies\[82\] (Figure 5).

Clinical data obtained only from anamneses and physical exams are also effective to classify CD and at the same time they help to provide guidance for the treatment\[96\]. CD may thus be divided in:

1. **Mild to moderate CD** - outpatients able to tolerate enteral feeding without dehydration, toxicity, abdominal discomfort, painful mass, obstruction or weight loss higher than 10% of bodyweight;
Prior to starting the IBD treatment, whenever possible it is advisable to get the following data from patients:

1. In case of UC – Evaluate: a) severity level: mild, moderate, severe or fulminant) using clinical, laboratorial and endoscopic data; b) the extension of inflammatory process using colonoscopy. Risk of perforation must be taken into consideration in case of severe cases; c) corticoid dependency.
2. In case of CD – Evaluate: a) activity level (mild, moderate or severe), using clinical, laboratorial and endoscopic data; b) extension of the disease by means of endoscopic and image exams; c) disease behavior (inflammatory, stenosing or penetrating), and d) corticoid dependency.

4. DRUG CLASSES

Salicylic derivatives

In this group of drugs, we have included sulphasalazine (SSZ) and salicylic derivatives. SSZ is unfolded in the colon by the bacterial azoreductase enzyme into sulphapiridine and 5-aminosalicylic acid (5-ASA). The latter is the active principle of this drug. Among the several action mechanisms of the 5-ASA action are modulation of proinflammatory cytokines secretion, inhibition of leukotriene and prostaglandin production, ability to scavenge free radicals and decrease oxidative stress, reduction of nuclear factor k-B (NF-kB), cell proliferation inhibition and apoptosis promotion. More recently, it has been shown that a great part of 5-ASA (mesalazine) action is due to its ability to activate PPAR-g (peroxisoma proliferatur-activated receptor-g), which plays a role in inflammation control, cell proliferation and apoptosis (63).

Side effects of SSZ are more commonly dose-dependent and related to sulphapiridine serum levels. Such effects occur mainly in individuals with low genetic ability of hepatic acetylation related to sulphapiridine serum levels. Such effects occur mainly in individuals with low genetic ability of hepatic acetylation (slow acetylators) in up to 45% of patients. These side effects include: abdominal pain, nausea, vomits, anorexia, cepahala, hemolysis, male infertility, etc. Less frequently, SSZ side effects may occur as a result of hypersensitivity (allergy or idiosyncrasy): fever, rash, lymphadenopathy, Stevens-Johnson agranulocytosis, hepatitis, pancreatitis, diarrhea exacerbation, etc. There are several types of controlled-release mesalazine (5-ASA) allowing the drug to be released in specific sites of the gastrointestinal tract as follows: a) microgranule mesalazine coated with ethylcellulosid: release of mesalazine irrespective of pH along the whole gastrointestinal tract, and more recently a prolonged-release oral mesalazine 2 g, that allow to take once a day (64); b) conjugation of 2 molecules of 5-ASA molecules (olsalazine) by an azo bond: release of the drug in the colon in a SSZ-like fashion (diarrhea in 10%-15% of cases owing to its secretagogue action on the small intestine and the colon); c) 5-ASA coated with acrylic resin (e.g., S or L eudragit) with...
active principle release from the proximal (eudragit L) and distal ileo (eudragit S) on and more recently a compound formula or acrylic resin (eudragit S) and two kinds of matrixes (lipophilic and hydrophilic) allowing mesalazine to be released in the colon when taken only once a day (MMX)\(^4(90)\), thus increasing patient’s adherence to the treatment.

Mesalazine is also available for topical use as suppositories, foam and enema. Most patients intolerant or allergic (80%-90%) to SSZ tolerate mesalazine, however some patients (10%-20%) present SSZ-like side effects when using mesalazine. A meta-analysis study published by Sutherland et al.\(^(88)\) at the Cochrane library showed that despite being less tolerated, SSZ is as effective in maintaining UC as mesalazine new formulations and is also less costly. For patients with mild/moderate UC in the left-sided hemicolon or in extensive areas, a combination of oral and topical mesalazine (>2 g/day) is more effective than the use of each of them separately\(^6(46, 73)\).

**Corticosteroids**

Corticosteroids (e.g., hydrocortisone, prednisone, prednisolone) are to date the drug of choice for moderate and severe cases of IBD.

In active UC and CD of moderate and mild intensity, oral prednisone (0.75-1 mg/kg/day, usually not necessary to exceed 60 mg/day) is indicated to induce the disease clinical remission. However, its use must be avoided for long periods (>2-3 months) even if administered at low doses. Corticosteroids withdrawal (weaning) must be gradual, reducing 10 mg/week up to 20 mg/day, followed by 5 mg/week until total withdrawal is achieved. If a relapse occurs during withdrawal, the corticosteroid dose may be increased to the same level as the dose before the one that caused relapse. In severe cases, inpatients may be given 100 mg IV hydrocortisone every 6 or 8 hours, followed by oral prednisone (without exceeding 60 mg/day) as soon as the patient is able to take it.

Corticosteroids usually induce clinical remission (70%-90% of cases after 4-6 weeks of treatment). However, they do not induce endoscopic and histologic remission in the same proportion as clinical remission (endoscopic and histologic remission approximately 30%\(^4(46, 61)\). In CD the frequency of corticosteroid-resistant (insensitive) and corticosteroid-dependent cases is high ranging from 8%-20% and from 15%-36%, respectively\(^6(2)\). In UC frequency of corticosteroid -resistance (29%) is usually higher than corticosteroid-dependence (<10%)\(^4(9)\).

Corticosteroids side effects are well known, mainly when used for prolonged periods of time, even at low doses: appetite stimulation and increase in bodyweight, edema, insomnia, emotional lability, psychosis, acne, Cushing syndrome, osteoporosis, osteonecrosis, growth stunt, hypothalamic-hypofisis-adrenal axis suppression, infections, myopathies, cataract, skin atrophy, striations, echymosis, fatty liver, diabetes, hypertension, glaucoma and acute pancreatitis\(^8(65)\). Due to these side effects, new corticosteroids have been developed in an attempt to reduce such effects. The most widely studied corticosteroid is budesonide which is metabolized fast (approximately 90%) in inactive products after its first passage through the liver. It is commercialized as an enema (2 mg/100 mL) and eudragit-L(3 mg) coated pills.

Oral budesonide side effects (9 mg/day) were similar to those in the placebo group, except for the “moon face”, more common in the budesonide group in comparison with the placebo (budesonide = 7%; placebo = 2%, \(P = 0.001\))\(^3(2)\). When compared to prednisone, budesonide’s side effects concerning corticosteroid therapy were less frequent in the budesonide group (33% of patients in the budesonide group and 55% in the prednisolone group (\(P = 0.003\))\(^7(6)\). Moreover, the hypothalamus-hypofisis-adrenal axis was less suppressed with the use of budesonide.

Corticosteroids should not be used as maintenance drugs. However, budesonide can be used for more prolonged periods of time (up to 6 months) when necessary. As soon as the patient presents signs of corticosteroid dependence (corticosteroid is necessary to maintain remission) or of insensitivity (nonresponsive to a corticosteroid dose of 0.75-1 mg/kg/day prednisone for 4-6 weeks), other alternatives (e.g. immunosuppressors such as azathioprine or 6-mercaptopurine) must be instituted.

**Immunosuppressors**

Azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX) and cyclosporine are included in this group of drugs.

**Azathioprine (AZA) and 6-mercaptopurine**

The exact mechanism of action of AZA and its metabolite, 6-MP has not been fully elucidated. What is known is that thioguanine nucleotides resulting from the drug metabolization prevent DNA and RNA formation. More recently, AZA and 6-MP have been shown to act via Rac1\(^7(60, 92)\) blocking CD-28 signaling molecules reducing Bcl-x synthesis and favoring CD4 lymphocytes apoptosis.

Immunosuppressors are effective to maintain remission in CD and UC and at the same time are useful at promoting corticosteroid withdrawal in corticosteroid-dependent patients\(^4(6)\).

AZA and 6-MP are first choice immunosuppressors followed by metotrexate (MTX) being indicated for CD in the following situations: a) resistance (insensitivity) or corticosteroid-dependence; b) for patients who need more than 2 courses of corticosteroids a year; c) for patients with early relapse after corticosteroid withdrawal (weaning) (<3 months); d) for patients submitted to bowel resection with remaining disease; e) for patients with fistulizing disease (penetrating); and f) for patients with extensive disease in the small bowel. In the case of UC immunosuppressors are indicated for patients: a) corticosteroid-dependent or -resistant; b) who need more than two courses of corticosteroids a year; and c) disease insensitive to the usual clinical treatment.

AZA and 6-MP dose is 2-3 mg/kg/day and 1-1.5 mg/kg/day, respectively. Both drugs have delayed action effects, thus a period of at least 3 months is required before the treatment may be considered as a therapeutic failure\(^7(9)\).

AZA and 6-MP side effects are related to bone marrow suppression which may occur in 3% of treated patients/year. Mielotoxicity depends on the dose used and the individual’s own ability to metabolize AZA and 6-MP adequately and it can be controlled with drug reduction or withdrawal. Leucopenia
is its more common manifestation. Mielotoxicity may occur in any phase of the treatment, but the initial dose adjustment requires closer attention\(^\text{30}\).

During this phase, hemogram, AST, ALT and amylase exams should be performed more frequently (every 15-30 days) and later every 3 or 4 months during the whole period of treatment.

Among other AZA and 6-MP complications, acute pancreatitis occurs in 1.6% of all treated patients, is not dose-dependent and occurs mainly in the first 3 or 4 weeks of treatment. Such complications are usually mild and improve with drug discontinuation. However they occur again almost universally in case the drug is reintroduced\(^\text{7}\).

Besides the side effects above mentioned, nausea, vomits, abdominal pains, allergic reactions such as fever, rash, myalgia and articulation pains may also occur.

Approximately 10%-15% of patients are intolerant to AZA or 6-MP. In this case they should be given an alternate drug (e.g., MTX). However, some AZA- intolerant patients may tolerate 6-MP and vice-versa.

Several drugs may interact with 6-MP metabolism such as 5-ASA (mesalazine), allopurinol, acetyl salicylic acid (ASS) and furosemide. Although aminosaliculates enhance the concentration of the active metabolite, in clinical practice they do not seem to interfere significantly in the management of AZA and 6-MP. Allopurinol on the other hand must be used with caution as it inhibits the drug metabolism main pathway.

In the long run, an increase in lymphoma risk becomes the major concern with the use of immunosuppressors. Nevertheless, despite the increased risk with the prolonged ASA and 6-MP use, an analysis using the Markov models to evaluate therapy impact over survival and life quality showed a gain in life expectancy and quality similar to that recommended for the use of rubella and hepatitis B vaccination and platelet antiagregant in patients with high risk for cerebral vascular accident\(^\text{49}\). Such benefit is higher in young patients since lymphoma risk in lower in this group and life expectancy higher, but it progressively decreases with age\(^\text{50}\).

AZA and 6-MP must be used over an undetermined period of time if the patient reacts well and if there are no complications. Their discontinuation is not necessary for patients to undergo elective surgeries\(^\text{47}\).

### Metotrexate (MTX)

Metotrexate is a folate antagonist and it interferes in DNA synthesis. It acts over cytokines and inflammatory mediators, blocking IL-1 binding to its receptor thus reducing IL-2, IL-6, IL-8, interferon-gamma and leukotriene B\(_2\) synthesis. MTX is indicated for patients with CD who need immunosuppressors and are azathioprine- or 6-MP-intolerant. Induction weekly doses are 25 mg intramuscularly, reducing to 15 mg/week after 3 to 4 months\(^\text{20, 21}\). In the initial phase, a monthly control of hemogram, AST, ALT, ALF and GGT is required. Later the control must be done every 3 months during all the treatment, while the patient's response is good and no complications occur\(^\text{69}\). MTX adverse reactions occur in 10% to 25% of patients: nausea, diarrhea, stomatitis, leucopenia, hair loss, increase in transaminases, hypersensitivity pneumonemia and hepatic fibrosis. Hepatic routine biopsy is not recommended and must be carried out in case of hepatotoxicity evidences. MTX is a teratogen and may induce miscarriage thus being contraindicated to women who wish to get pregnant.

### Cyclosporine

Cyclosporine acts by reducing interleukine-2 (IL-2) production by T-helper cells. It has been effective as a “rescue treatment” of severe unresponsive UC after 5-10 days of intravenous corticotherapy. The current recommended dose is 2 mg/kg/day\(^\text{97}\) IV, with continuous infusion for 1 to 2 weeks, followed by the oral administration of another maintenance drug. At short-term results are favorable ranging from 60% to 80%. At medium and long term, however, the drug does not elicit good results unless an immunosuppressor such as AZA or 6-MP is introduced. The major drawbacks to cyclosporine therapy are: need for serum levels monitoring, interaction with other drugs and mainly its toxicity. Plasma levels between 150-300 ng/mL measured by radioimmunoassay with monoclonal antibody or HPLC (high-performance liquid chromatography) are considered safe. Cyclosporine is metabolized in the liver cytochrome P-450 and therefore drugs that induce it (such as cimetidine, rifampicin, trimetoprim, carbamazepine, phenobarbital, phenytoin, octreotide) may decrease cyclosporine blood concentration and the ones that inhibit it (e.g., verapamil, floracnozale, etoconazole, claritromicine, erythromicne, corticosteroids, metolopramide, choloroquine) may enhance it. Side effects occur frequently and may reach 50%. Listed in order of frequency they are: paraesthesia, blood hypertension, hypertrichosis, kidney failure, cepalea, opportunist infections, gingival hyperplasia, dizziness and anaphylaxis. Grand mal seizures may occur in patients with low plasma levels of cholesterol (<120 mg/dL).

### Biological therapy

This new approach is generically called biological therapy as it acts on mediators and natural and physiological phenomena.

Many biological therapies are still being tested\(^\text{69}\). However, results with the anti-TNF antibody (antibody against tumoral necrosis) therapy are widely known. Drugs already commercialized in Brazil such as infliximab (chimeric anti-TNF, 75% human) and adalimumab (anti-TNF 100% human) are included in this category.

Biological therapy has been increasingly used to treat UC and CD, however it must be applied to moderate and severe cases or when the patient is insensitive to other treatments. Extraintestinal manifestations insensitive to other treatments may also be treated with anti-TNF even without signals of bowel inflammatory activity. Likewise, situations in which life quality is severely compromised such as in the case of anal and/or perianal fistulae can be treated early with biological therapy.

Anti-TNF side effects usually occur in less than 10% of cases and in some trials it was not higher than that observed in the placebo group\(^\text{23, 32}\). The most commonly anti-TNF side effects mentioned are: infusion reactions, upper respiratory tract infections, bronchitis, pharyngitis, fever, cepalea,
nausea, abdominal pain; less frequently: dizziness, thoracic pain, arthralgia, delayed sensitivity reactions (abdominal or perianal), pneumonia furunculosis, bowel obstruction, hemolytic anemia, cardiac dysfunction, drug-induced lupus (positive anti-DNA), and increased risk of lymphoma.

Tuberculosis reactivation may occur post anti-TNF use thus PPD and chest X-ray are mandatory prior to the infusion(101). Patients with PPD >5 mm and normal chest X-ray must take isoniazide for 6 months and anti-TNF may be started after the 1st month of this treatment. If chest X-ray indicates active disease, treatment with triple scheme is recommended before the infusion. Similarly, the drug must be avoided in patients with functional class III/IV heart failure. There is no formal contraindication of anti-TNF use for patients with bowel stenosis69.

Something vital that has been described about biological therapy is that it can promote endoscopic and histologic improvement, which in the future may be translated as a positive impact over the disease natural history.

Infliximab recommended dose is 5 mg/kg at 0, 2 and 6 weeks, IV followed by a maintenance dose every 8 weeks(39). If the patient loses response during maintenance treatment, dose may be increased to 10 mg/kg or the interval between infusions may be reduced (every 4-6 weeks)(40). Approximately 30% of patients using infliximab for 3 years will require a dose increment or to decrease interval between infusions.

Adalimumab induction dose regimen is 160 mg via subcutaneous injection, followed by 80 mg after 2 weeks(39). During the maintenance regimen, drug must be used at 40 mg every 2 weeks(14, 80).

The mechanism of anti-TNF action is complex and requires more than one phase. The anti-TNFs bind to the circulating soluble TNF, preventing it from playing its pro-inflammatory role. They also neutralize TNF receptors, resulting in the signaling block of this cytokine, thus reducing the inflammatory process. Moreover, anti-TNFs bind to the TNFs bound to producing membrane cells (transmembrane TNF) and produce reverse signaling which inhibits TNF production and induces apoptosis of cells producing TNF. When anti-TNF binds to receptors or transmembrane TNF, it facilitates complement activation and fagocitosis of the immunocomplex(69).

Presently the best time to use anti-TNF therapy has been widely discussed. D’Haens et al.(18) advocate the early use of infliximab, when diagnosis is made, as they consider that this early intervention may reduce the future complications caused by the disease. However, although their study reports that this therapeutic option induces increased clinical remission in the first year and endoscopic one in 2 years of follow-up when compared with conventional strategies, their study lacks long-term data showing that this more aggressive therapy indeed causes a great impact on CD natural history. Therefore the present consensus guidelines recommend that until more data are available addressing this issue biological therapy be used for insensitive cases of CD and UC.

It is not possible to establish a definite and consensual conduct concerning the use or not of immunosuppressors associated with infliximab in adults using current data(98). Thus the physician must consider the patient’s clinical history and decide on a suitable conduct in each case.

5. CLINICAL TREATMENT FOR CD ACCORDING TO LOCATION AND SEVERITY OF DISEASE

Mild ileocecal CD

Acute phase treatment must be carried out preferably with oral budesonide, 9 mg/day (Grade A), as it is superior to placebo(32, 66, 84) and mesalazine(90, 91) and as it presents fewer side effects despite being less effective than prednisone(66, 84).

Oral mesalazine, 4 g/day, reduces CDAI, but clinical benefit is debatable since reduction is very small(40). Doses lower than 4 g/day do not present any benefit.

After remission, patients may remain without maintenance treatment and be given only symptomatic drugs. Mesalazine maintenance treatment is not superior to placebo(91) and cannot be recommended (Grade B).

Moderate ileocecal CD

Oral treatment with budesonide may be attempted in some cases, but oral prednisone, 0.75-1 mb/kg/day (not exceeding 60 mg/day) has superior efficacy(66) (Grade A).

Severe ileocecal CD

Initial treatment must be made with systemic corticosteroid either via oral or parenteral, considering the patient’s previous history. Patients with early relapse or those in need of more than two courses of corticosteroids a year must be given immunosuppressors (AZA or 6-MP). For those who relapse even when the correct dose of immunosuppressors is administered, anti-TNF must be considered. Surgical treatment may be required mainly for patients with stenosing disease behavior or other complications (e.g. abscesses) (Grade C).

CD of the colon

Treatment with sulphasalazin (>3 g/day) is superior to placebo and may be used for mild cases, with colon injury(56, 80) (Grade A). More severe cases must be treated with systemic corticosteroid such as prednisone. Use for immunosuppressors and anti-TNF is similar to that previously discussed. Patients with colon lesions respond better to therapy with anti-TNF (Grade C).

Patients with distal lesion may receive topical therapy such as enema and suppositories, associated with the oral therapy (Grade C).

Oral antibiotics (oral metronidazol, 750-1000 mg/day and oral ciprofloxacin, 1 mg/day)(71, 87) induce response superior to placebo and are a useful alternative for patients at high risk of complications with the use of corticosteroid, such as diabetic and hypertensive patients (Grade B).

Extensive small bowel CD (>100 cm)

Extensive small bowel CD must be treated with systemic corticosteroids in the acute phase and treatment with oral immunosuppressors (AZA or 6-MP) must have been already initiated. Most of these patients are severely malnourished and will benefit from adjuvant treatment with parenteral...
or enteral nutrition. Anti-TNF treatment is a worthwhile alternative and may be indicated more liberally for patients with severely compromised nutritional status. Patients with multiple stenoses, insensitive to the initial clinical treatment must undergo surgical procedures, preferably by means of stenoplasies thus avoiding extensive resection of the small bowel and the risk of short bowel (Grade C).

CD of the upper gastrointestinal tract

Patients with esophagus and stomach lesions must be given high doses of proton pump inhibitors (e.g., omeprazol, 80-160 mg/day) associated or not with systemic corticosteroids during acute phase. Long-term treatment must be done with immunosuppressors or biological therapy. Stenoses might be approached through endoscopic dilations (Grade C).

Anal and/or perianal CD

Patients with fistulizing (penetrating) CD are considered more critical irrespective of luminal inflammatory activity and require specific evaluation and approach. Perianal fistula examination must be carried out under narcosis and using imaging methodologies (preferably nuclear magnetic resonance) which allow the evaluation of the fistulous trajectory and the exclusion of adjacent collections or in the fistula trajectory. If collections are present, they must be surgically approached with drainage and seton placement before anti-TNF treatment is started (Grade C).

Initial treatment includes the use of antibiotics (ciprofloxacin and/or metronidazol) in the above mentioned doses, associated with immunosuppressors for a prolonged time (Grade B). Anti-TNF is efficient and is indicated for the treatment of complex fistulose or those unresponsive to the initial treatment (Grade C). Moreover, it is currently the most efficient treatment for anal and/or perianal fistulae with 70%-80% rates of clinical remission and 40%-60% rates of full sealing of fistulae (Grade A). Entero-vesical, entero-cutaneous and rectum-vaginal fistulae do not present a good response to anti-TNF therapy like the anal and/or perianal fistulae (Grade C).

6. CLINICAL TREATMENT FOR UC ACCORDING TO SEVERITY AND EXTENSION OF DISEASE

UC choice treatment is with aminosalicylates and the choice for the best formulation depends mainly on the extension of the disease, whereas need for drug titration will depend on the severity of disease (Grade A).

Distal UC (proctitis and proctosigmoiditis)

Choice treatment for acute proctitis is done with suppositories 1 g/day for 4-6 weeks. Mesalazine suppositories are more efficient than topical treatments with corticosteroids, which must be limited to patients intolerant or insensitive to mesalazine. Mesalazine enema when well applied may reach the splenic angle and is the favorite drug to treat proctosigmoiditis, but it promotes a lower concentration of 5-ASA in the rectum when compared with suppositories. Non responsive patients may be prescribed a treatment regimen associated with oral aminosalicylates or even systemic corticosteroids (Grade B).

Maintenance treatment may be carried out with mesalazine suppositories 3 g/week (1 g, 3 times a week) and may be discontinued after 1 year without relapses. Risk of developing neoplasia is similar to the general population (Grade B).

Left-sided hemicolon UC

In this case treatment may be done only via the rectum using enema mesalazine, but many patients will require treatment with oral aminosalicylates (>2-3 g/day). The association of oral and topical mesalazine is superior to the treatment with mesalazine administered orally or by topicaly. Meta-analysis studies showed that an increase in mesalazine doses improves response and decreases the length of bleeding period (Grade B). Prednisone in its usual dose must be started if bleeding continues for more than 2 weeks with the suitable use of aminosalicylates. Every patient must receive maintenance treatment with aminosalicylates over an undetermined period of time (SSZ or mesalazine) via oral doses higher than 2.4 g/day (Grade A). Besides decreasing number of relapse episodes, maintenance treatment reduces risk of colorectal cancer

Pancolitis

Patients with inflammation extending up to the proximal transverse colon or beyond are considered as suffering from pancolitis (universal or extensive colitis). Generally, such patients are more critical and require oral treatment associated with topical treatment. Similarly to patients with left-sided colitis, treatment with prednisone at the usual dose must be started if bleeding persist for more than 2 weeks after the beginning of treatment with aminosalicylates (>2-3 g/day) (Grade A). If the patient is already using an aminosalicylate (mesalazine or SSZ) or an immunosuppressors, corticosteroids must be started initially. All patients must receive maintenance treatment with aminosalicylates at doses higher than 2.4 g/day.

Severe and fulminant UC

These patients face a real risk of death and should be admitted to hospital to undergo intensive treatment. The choice treatment is parenteral corticosteroids (e.g., hydrocortisone, 100 mg IV, 3-4 times/day). Corticosteroid response assessment must be done between 3 and 7 days and rescue or surgical treatment is indicated in case of therapeutic failure (Grade B).

Besides corticosteroid treatment it is important to: a) correct hydroelectrolytic disturbances, specially potassium and magnesium; b) research C. difficile toxin; c) institute enteral diet; d) suspend any anti-inflammatory, anticholinergic, anti diarrheal or opiate drug that the patient might be taking; e) carry out blood transfusion if hemoglobin is lower than 10 g/dL; f) start prophylactic subcutaneous heparin (Grade B).

Rectosigmoidoscopy without prior bowel preparation in such cases is safe and not only does it make it possible to confirm inflammation but also to rule out cytomegalovirus infection. Fulminant cases with or without toxic megacolon must be clinically and radiologically evaluated and be supervised by a coloproctologist. In such cases, rescue therapy must be carried
out with cyclosporine IV\(^{(54, 97)}\), or infliximab\(^{(59, 77)}\) (Grade A). Both are efficient and have advantages and disadvantages. Cyclosporine acts more quickly but has a higher number of side effects, some of them severe and irreversible. On the other hand, infliximab therapy has fewer side effects but time to respond seems to be longer. However, there are no studies directly comparing cyclosporine rescue therapy vs anti-TNF thus precluding a choice based on scientific evidences. Taking into consideration current experience with infliximab and cyclosporine side effects this consensus guidelines recommend that the initial rescue therapy be done with infliximab and that colectomy be indicated in case rescue treatment with one of these drugs fails. Indication for colectomy must be evaluated in 24-72 h; however many times very critical patients who cannot wait for the drugs to act must be initially treated with colectomy.

All patients undergoing successful rescue treatment must receive an oral aminosalicylate (SSZ or mesalazine) besides an immunosuppressors and/or anti-TNF. However, the long-term possibility to preserve the colon is not promising (Grade C).

### 7. SPECIAL SITUATIONS AND CONSIDERATIONS

#### Refractory proctitis

A small percentage of patients with non-specific proctitis show unproportional severity to the macroscopic extension of the disease and will require oral drugs, including aminosalicylates, systemic corticosteroids, immunosuppressors or even biological therapy. In this case it is important to review symptoms, the UC diagnosis itself, previous treatments and its adherence to it and to have a recent colonoscopy with serial biopsies. If symptoms persist for more than 4-8 weeks despite adequate therapeutic conduct, the treatment must follow the established guidelines for extensive or severe UC (Grade C).

#### Early recurrence of IBD

Therapeutic decision is different for the patients with the first “acuitation” crisis and the other subsequent crises. Previous treatments, interval between relapses and their frequency must be considered. Therefore patients relapsing in less than 3 months after corticosteroid weaning must be submitted again to treatment induction and be given oral immunosuppressors (AZA or 6-MP) as an attempt to avoid future relapses\(^{(40)}\) (Grade B).

#### Corticosteroid-dependant IBD patients

We consider corticosteroid-dependant all patients responding to corticosteroid treatment in the acute phase but relapsing during corticosteroid withdrawal. So, as to maintain disease in remission or at low activity levels, such patients need variable corticosteroid doses and usually have complications due to the prolonged use of corticosteroids. For this group of patients, treatment with immunosuppressors\(^{(2, 4, 60)}\) or anti-TNF\(^{(14, 48, 77, 80, 81)}\) is indicated to assist in the corticosteroid withdrawal (Grade A). Patients not using immunosuppressors must take AZA/6-MP or MTX, whereas for those who already use these drugs or are intolerant to them, anti-TNF therapy is indicated.

### Corticosteroid-refractory IBD patients

We consider corticosteroid-refractory patients those who do not respond to the adequate systemic corticosteroid treatment dose (0.75-1 mg/kg/day) and period (4-6 weeks) and after other complicating factors have been excluded (e.g., abscesses, cytomegaloviruses, \textit{C. difficile}, etc). For the therapeutic approach of corticosteroid-refractory patients, the severity of disease must be considered. Also it is important to bear in mind that immunosuppressor’s time of action is longer (3-4 months). On the other hand, anti-TNF acts more quickly and is the choice treatment for these patients. Patients already using an immunosuppressor must take anti-TNF as well and in case of UC surgery must be considered. Many patients benefit from adjuvant nutritional therapy preferably via an enteral feeding tube (Grade C).

#### Extraintestinal manifestations\(^{(8)}\)

Gangrenous pyoderma may be treated with systemic corticosteroids, immunosuppressors or anti-TNF at the doses usually prescribed for underlying diseases. Metastatic CD sometimes is more severe than the underlying disease and may be treated with systemic drugs such as immunosuppressors or biological therapy. Articular manifestations must be treated concomitantly with the underlying disease, using titration as necessary. Many times extraintestinal manifestations are as important or more than the intestinal manifestations and must be treated with the same drugs including biological therapy regardless of luminal inflammatory activity such as in the case of axial arthritis (sacroileitis, ankylosing spondilitis) (Grade C).

#### Pregnant women

The present consensus guidelines consider disease remission during pregnancy the most important isolated factor for a complication-free pregnancy for the mother and for the unborn child. It is equally important that the patient get pregnant during a remission period. IBD patients have a higher prevalence of pre-term births with an increased risk for miscarriages and low birth weight babies regardless of the used drugs\(^{(15, 55)}\) (Grade B). Remission patients using sulphasalazine, mesalazine, azathioprine or anti-TNF are regarded as safe patients and should remain so during all the pregnancy. MTX is contraindicated during pregnancy. Ciprofloxacin may be avoided as well, but metronidazol may be used for a short period but must be avoided before the birth (3rd trimester) (Grade C). Corticosteroids may be used when necessary as well, but physicians must take extra care with the possible onset of diabetes.

Vaginal birth should be the first choice, except in face of ileoanal pouch or active perianal disease. An episiotomy may be performed.

#### Nutritional aspects in IBD

As many as 80%-90% of inpatients with CD and up to 60%-70% of inpatients with UC have any kind of nutritional deficit. These percentages drop to 50%-60% in CD and 40%-50% in UC in the case of outpatients. Enteral nutrition should be the preferred route while parenteral nutrition should be limited to
patients who cannot be fed by means of enteral diet (e.g., bowel obstruction). Polymeric (containing whole proteins), oligomeric (containing peptides) or monomeric (aminoacids) diets are equally effective.\(^8, 10\) (Grade A). Enteral nutrition therapy in adults is inferior to the corticosteroid treatment in the acute phase and should be used as an adjuvant during pre- and post-operative care. It may also be considered as an alternative in case of refractory IBD, mainly CD. For children and adolescents, exclusive nutritional therapy may be used as a primary measure for CD treatment thus avoiding the use of corticosteroids.

**Probiotics in IBD**

Random clinical trials do not favor the use of probiotics in CD\(^{13, 72, 83, 99}\); thus not being recommended for this disease (Grade B). Similarly, it should not be used in CD post-operative care. However, UC studies point to the benefits of using probiotics as a maintenance therapy. \(E. \) coli Nissle in concentrations higher than 10\(^8\) and VSL#3 (10\(^8\)) are superior to placebo\(^{(20)}\) and similar to aminosalicylates to maintain remission in UC\(^{34, 70}\) (thus being an alternative for maintenance treatment in patients intolerant or allergic to aminosalicylates (Grade B). Probiotics are also effective for the treatment\(^{(29)}\) and prevention of chronic pouchitis\(^{(30)}\) after total proctocolectomy with ileoanal pouch.

**Colon cancer screening in IBD**

The following are considered risk factors for the development of cancer in IBD: a) long-term disease; b) presence of associated primary sclerosing cholangitis; c) family history of colorectal cancer; d) extensive disease; e) previous history of colonic dysplasia (Grade C).

Colorectal cancer screening using colonoscopy in UC (pancolitis) is indicated after a 8-10 year progression and in left-sided colitis, after 12-15 years of illness. Screening must performed using colonoscopy every 3 years in the 2nd decade, every 2 years in the 3rd decade and yearly in the 4th decade of illness together with 4-quadrant biopsies of non-inflamed mucosal at every 10 cm of colon, in the whole colon in association with biopsies of suspected areas. Chromo colonoscopy with biopsy of suspected area is a valid alternative to multiple biopsies. Patients with primary sclerosing cholangitis have high risk of developing colorectal cancer thus needing to undergo colonoscopy associated with yearly biopsies soon after diagnosis. Patients with rectitis should be screened similarly to the normal population.

Findings of high grade dysplasia during UC remission phase, if confirmed, will imply in total proctocolectomy (Grade C).

In colon CD, despite not being fully established, screening must be also considered after 8-10 years of disease progression (Grade C).

**8. SURGICAL TREATMENT**

**Surgical recommendations for UC**

Decision about surgical approach in patients suffering from IBD must be made considering the gastroenterologist’s, the coloproctologist’s and the patient’s opinion.

In the case of UC, surgery must be limited to patients not responding clinically well to drug therapy. In addition to clinical “untreatability” other elective indications are: growth stunt in children, extraintestinal manifestations (gangrenous pyoderma) and the presence of high grade dysplasia or adenocarcinoma in the colorectal segment.

Emergency surgical indications in UC are: hemorrhage, bowel obstruction, toxic megacolon and bowel perforation.

Surgical treatment must be performed after both the gastroenterologist and the coloproctologist indicate surgery and with the patient’s agreement.

The patient must be previously informed and warned that an ostomy might be performed during the surgery.

During pre-operative exams, the stomaltherapist or the coloproctologist must establish the site for ostomy placement.

A midline incision is usually best when a laparotomy is required.

Surgery technical options (advantages and disadvantages) must be clearly explained to patients with elective indication. When an ileoanal anastomosis is indicated, the patient must be warned about the possibility to develop pouchitis.

The choice procedure for patients with fulminant colitis or toxic megacolon without improvement with conventional treatment must be total colectomy with rectum burying and terminal ileostomy. An alternative to this technique is performing a terminal ileostomy and a mucosal fistula.

In presence of fecal or purulent peritonitis (pelvic sepsis) primary anastomosis must be avoided similarly to cases of severe malnutrition.

Total proctocolectomy with definitive ileostomy is indicated for pancolitis (also known as universal colitis) associated with low rectal cancer and/or fecal incontinence.

Clinical untreatability is the main indication for total rectocolectomy and an ileoanal anastomosis with reservoir (ileal pouch).

Incidence of sexual dysfunction when an ileal pouch surgery is performed is lower than in cases of rectal resection due to tumors.

The main disadvantages of total colectomy with ileorectalanastomosis are: risk of rectal cancer, high rates of relapse and need for careful outpatient follow-up.

If corticosteroids were used for 4 months before surgery, an endovenous infusion of hydrocortisone must be applied during the surgery.

Videolaparoscopy should be used in specific cases, avoiding its use with the complex ones.

Malignization risk has been increasing in patients with UC with more than 10 years of progression, mainly with pancolitis and early onset of disease.

In case of severe dysplasia, the glass slide must be reexamined and if positive, surgical treatment is recommended.

**Surgical recommendations for CD**

Crohn’s disease surgical treatment must take into consideration disease location, severity of symptoms (activity) and the patient’s nutritional status.
Decision for a surgical procedure must be the result of a common agreement between gastroenterologist, coloproctologist and patient.

During the preoperative evaluation, the patient must be warned about risks of a possible ostomy.

Colostomy site marking must be done during preoperative evaluation by a stoma therapist or coloproctologist.

If corticosteroids were used during the 6-month period prior to the surgery, during the surgical procedure and post operative period, patients must be given this drug as a means to prevent acute adrenal insufficiency.

Corticosteroids in high doses and for over a prolonged period of time are the only drug that can negatively interfere with the surgery outcome.

Ponderal loss higher than 15% of bodyweight in 3 months and hypoalbuminemia (<2.5 g/dL) are risk factors for surgical complications.

The median incision must the choice for patients requiring a laparotomy both in elective and emergency settings.

Videolaparoscopic resection should not be performed in presence of very complex diseases and previous surgeries. It should be limited to specific cases.

Main indications for elective surgeries are: clinical "untreatability", growth stunt, extraintestinal manifestations, high grade dysplasia, presence of adenocarcinoma, intestinal obstruction, refractory intestinal suboclusion, internal and external fistulae, palpable abdominal mass and perianal disease.

CD intestinal resections must be limited to the macroscopically compromised area (economical resection).

Enteroplasty or economical resection should be the chosen techniques when the disease is located in the small bowel.

When the small bowel has multiple stenoses located in a short section, primary resection is the best therapeutic alternative.

Manual or mechanical latero-lateral anastomosis should be preferred as it presents lower rates of symptomatic relapse than the termino-terminal one.

Surgical drains must be avoided in CD surgery.

In case of ileal or ileocecal CD with intestinal obstruction, resection must be performed using mechanical latero-lateral anastomosis, whereas enteroplasty may be used in specific cases of anular segmentar stenosis.

Freezing biopsies is not necessary when an enteroplasty is performed.

Dehiscence rates with enteroplasty are not higher than intestinal resection with mechanical latero-lateral anastomosis.

Resection with mechanical latero-lateral with ascending-ileum is recommended in case of severe acute ileitis (with stenosis, mesentiritis, panniculitis).

In presence of acute ileitis with a discrete inflammatory process associated with appendicitis, an appendicectomy must be performed. If the appendix is normal, no resection should be performed. However appendicectomy is recommended for patients who cannot undergo follow-up.

In case of an intraperitoneal abscess, whenever possible a diagnostic emptying image-guided puncture should be performed in association with antibiotic therapy. Surgery must be performed at a later time.

In presence of an internal (entero-vesical or colonvesical) or external (enterocutaneous or colocutaneous) abdominal fistula, the choice conduct is a laparotomy with resection of the compromised section.

A loop ileostomy without resection (as an isolated surgery) must be avoided for the treatment of Crohn's pancolitis and perianal disease.

A partial colostomy must be the choice treatment in case of segmental diseases located in the colon (<1/3 or 1/4 of compromised colon) without concomitant perianal disease.

Total colectomy with ileo-rectal anastomosis is the best therapeutic alternative when two segments separated from the colon are affected by active CD and in absence of concomitant perianal disease.

Total colectomy is the suitable treatment for severe left-sided colitis.

Primary anastomosis must be avoided both in case of pelvic and peritoneal sepsis and in presence of severe malnutrition.

Stenoplasties must be avoided in the colon.

Ileal pouch should not be recommended as a rule in CD – only in specific cases (severe pancolitis in young individuals who refuse to undergo ostomy and do not present perianal disease).

Recommendations for emergency surgery in CD are: acute obstructed abdomen, severe and persistent hemorrhage, intestinal perforation, toxic megacolon and acute ileitis.

In the cases of toxic megacolon refractory to conventional measures (hydrocortisone, cyclosporine and biological therapy) total colectomy without anastomosis is the recommended surgery. Reconstruction should be performed with the burying of rectum or mucous fistula and a terminal ileostomy should be performed.

Endoscopic dilations of stenoses can be used in CD, although they might be associated with complications.

Anal and perianal disease should only be treated with surgery when symptomatic.

In case of severe ano-rectal perianal CD, hyperbaric oxygen therapy is a useful alternative, and it may be associated with antibiotics, immunosuppressors and anti-TNF.

Ano-rectal perianal surgery in CD must be conservative performed with abscess drainage and seton placement, always associated with clinical measures. Sphincterotomies should be avoided. Severe perianal disease should not be treated only with ostomy.

**Prevention of postoperative relapse in CD**

Main risk factors for postoperative relapse are: smoking, pancolitis, small bowel extensive disease, fistulizing perianal disease and absence of complementary drug therapy.

Patients must be strongly advised to discontinue smoking early and they should be helped to reach this objective.

During terminal ileum CD postoperative a colonoscopy is recommended between 6 and 12 months post surgery and the Rutgers score[9] must be used as a guideline for therapeutic conduct as follows: i0 – absence of ileal lesions; i1 – fewer than five aphthous ulcers less than 5 mm in length; i2 – more than five aphthous ulcers with normal mucosa between the lesions...
OR larger focal lesions OR lesions confined to the ileocolonic anastomosis less than 1 cm in length; iii diffuse aphthous ileitis with diffusely inflamed mucosa; iv diffuse inflammation with larger ulcers, nodules and/or narrowing. CD patients referred to ileocolic surgery presenting HIGH risk for postoperative recurrence (e.g. older than 30 years of age, smokers, with penetrating disease, previous resection(s), resections more than 100 cm in length, use of corticosteroids during the last 3 months, short-lasting disease) should take metronidazol together with AZA or 6-MP at regular doses. AZA or 6-MP may be started approximately 2 weeks after surgery. A colonoscopy must be done 6-12 months post surgery and the Rutgers score must be applied: from cases i0 to i2, it is recommended to maintain AZA or 6-MP; in cases i3 or i4, biological therapy must be considered. Moreover, patients should undergo a colonoscopy every 1-2 years. Patients with LOW risk for postoperative recurrence (those not included in the high risk group) are recommended not to receive any drugs. A colonoscopy should be performed 6-12 months later and the Rutgers score should be applied. Cases included in the i0 to i2 groups may remain unmedicated, whereas in cases i3 or i4 the introduction of AZA or 6-MP is recommended at regular doses. Next, a control colonoscopy every 1-2 years is recommended.

**Pouchitis**

Pouchitis crises usually increase during the postoperative period. Approximately 30% to 50% of patients undergoing UC ileal pouch operation will develop pouchitis after 10 years of follow-up. Pouchitis diagnosis must be based on clinical, endoscopic and histological evidences. Differential diagnosis must be done based on ciffits, pelvic sepsis and irritable pouch syndrome.

Metronidazol at 400 mg, 3 times a day for 2 weeks is the choice treatment. In case of intolerance, ciprofloxacin 500 mg, twice a day for 2 weeks should be administered. If antibiotics prove to be ineffective, other treatments may be used.


RESUMO – Este é o primeiro Consenso Brasileiro sobre a Doença Inflamatória Intestinal, realizado pelo Grupo de Estudos sobre a Doença Inflamatória Intestinal do Brasil (GEDIIB), e aborda o tratamento da doença de Crohn e da retocolite ulcerativa durante a fase de agudização e remissão. A primeira parte do texto traz uma revisão das principais drogas utilizadas no tratamento da doença inflamatória intestinal, bem como seus mecanismos de ação e os cuidados necessários durante seu uso. Na segunda parte do trabalho, é apresentada a opinião do grupo sobre as abordagens clínicas e cirúrgicas mais recomendadas com base no grau de atividade da doença, na sua localização e no comportamento da doença. As recomendações emitidas pelo GEDDIB foram amplamente discutidas em várias reuniões científicas, com ativa participação de todos os membros do grupo e baseadas em evidências científicas da literatura.


REFERENCES


